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Management of Malignant Bowel Obstruction Associated With GI Cancers

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ASSOCIATED CONTENT

See accompanying commentaries on pages 435 and 437

Abstract

For many patients with GI malignancies, the seeding of the abdominal cavity with tumor cells, called peritoneal carcinomatosis, is a common mode of metastases and disease progression. Prognosis for patients with this aspect of their disease remains poor, with high disease-related morbidity and complications. Uniform and proven practices that provide optimal palliative care and quality of life for these patients are needed. The objective of this review is to critically assess the current literature regarding palliative strategies in the management of peritoneal carcinomatosis and associated symptoms in patients with advanced GI cancers. Despite encouraging results in the select population where cytoreductive surgery and intraperitoneal chemotherapy are indicated, the majority of patients who develop peritoneal carcinomatosis in the setting of GI cancers have poor prognosis, with malignant bowel obstruction representing a common terminal phase of their disease process. For all patients with peritoneal carcinomatosis, aggressive symptom control and early multimodality palliative care as further outlined should be sought.

INTRODUCTION

Advances in systemic therapy, patient selection, and supportive care have improved survival for patients with metastatic colorectal and gastric cancer.[1,2] Unfortunately, the development of peritoneal carcinomatosis in many patients with GI malignancies remains a poor prognostic finding, with complications that preclude or interrupt systemic therapy secondary to declining performance status and recurrent bowel obstruction.[3] Clinical management of peritoneal carcinomatosis is challenged by recurrent bowel obstruction, ascites, visceral pain, and malnutrition. Treatment of peritoneal carcinomatosis may range from cytoreductive surgery and intraperitoneal chemotherapy to supportive care alone. Review of the data supporting cytoreductive surgery or intraperitoneal chemotherapy is beyond the scope of this discussion. We review the literature regarding evidence-based palliative strategies, including management of bowel obstruction, malignant ascites, optimization of nutrition, and pain control, with the goal of providing optimal palliative care and quality of life for patients with peritoneal carcinomatosis.

CYTOREDUCTIVE SURGERY AND INTRAPERITONEAL CHEMOTHERAPY

The benefit of cytoreductive surgery and intraperitoneal chemotherapy, originally demonstrated in ovarian cancer, was later established as the accepted standard-of-care treatment of low-grade mucinous tumors of the appendix.[4] However, for peritoneal carcinomatosis associated with other GI malignancies, the palliative role of cytoreductive surgery/intraperitoneal chemotherapy remains controversial. This approach

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should be reserved for patients with a good functional status and the ability to tolerate potential surgical morbidity. It should also be performed at a high-volume center with experience in this procedure, preferably as part of a clinical trial.[5]

BOWEL OBSTRUCTION

Malignant bowel obstruction (MBO) is a prevalent and often terminal complication of peritoneal carcinomatosis, necessitating an interdisciplinary approach to palliative care. Although the incidence of malignant bowel obstruction is highest in patients with advanced epithelial ovarian carcinoma, the mechanistic differences in pathophysiology and subsequent management of this disease entity remain outside the scope of this review. Currently, limited prospective data exist to support a standardized clinical management strategy, leaving the majority of decision making influenced by provider preference and resource availability. The ongoing Southwest Oncology Group 1316 trial (ClinicalTrials.gov identifier: NCT02270450), comparing best supportive care with surgical intervention for GI malignancy–related MBO, will further define the role of surgery in these patients. In the interim, the following recommendations are largely based on published institutional experiences.

MBO is defined by clinical and radiographic evidence of a bowel obstruction, distal to the ligament of Treitz, secondary to either a primary intra-abdominal tumor (metastatic colorectal cancer, 25% to 40%; gastric cancer, 6% to 13%) or, rarely, an extra-abdominal malignancy (ie, melanoma and breast) with peritoneal metastasis.[6,7] Mechanisms of MBO include mechanical (related to extrinsic bowel compression or endoluminal obstruction), functional (associated with tumor infiltration of autonomic nerve plexuses), paraneoplastic syndromes, and drug-induced ileus. However, a broad differential must be considered, as presumed MBO is secondary to nonmalignant etiologies in approximately 25% of patients with peritoneal carcinomatosis (Table 1).[8] The pathophysiology of MBO involves a cycle of voluminous digestive secretions, third spacing of fluids, hypovolemia, bowel distension, and high-frequency peristalsis, with resultant intestinal epithelial damage, inflammation, and amotility.[9] Patients typically present with colicky abdominal pain, anorexia, nausea, and vomiting depending on the level of obstruction (ie, small bowel *v* distal colon). Symptoms of obstipation, an inability to defecate or pass flatus, indicates a complete obstruction, whereas paradoxical diarrhea and fecal incontinence (ie, overflow diarrhea) suggest partial obstruction.[10]

The current diagnostic gold standard for MBO is a contrasted computed tomography scan of the abdomen and pelvis; however, given the overall accessibility, low cost, and reasonable sensitivity to detect complete obstruction, plain abdominal radiography is a pragmatic initial evaluation tool for suspected MBO. In addition to the location and mechanism of the obstruction, oncologic variables (eg, performance status, response to prior therapy, overall prognosis, advanced directives) need to be considered to optimize palliative treatment of MBO. The ultimate goal is to support the patient through disease control or symptom palliation, which may or may not include surgical or medical interventions.

SURGICAL MANAGEMENT

Although surgical consultation may be warranted for emergent complications (eg, volvulus, ischemia, and perforation), there is no high-quality evidence describing an optimal therapeutic approach for the majority of patients presenting with MBO. Even for surgical emergencies, a nonoperative approach may still be warranted if the patient's overall disease prognosis or goals of care are inconsistent with aggressive measures. The majority of surgical recommendations are largely derived from data in patients with peritoneal carcinomatosis associated with ovarian cancer. Review of these early, nonrandomized studies suggests surgical intervention may be feasible for obstructions with radiographic evidence of a transition point and absence of extensive carcinomatosis or large-volume ascites.[11]

In the largest pooled analysis of surgical outcomes (43 trials, 4,265 patients), clinical resolution of MBO ranged from 27% to > 68%, though multiple studies failed to clearly define this parameter.[12] Rates of reobstruction, shown to be a valuable prognostic indicator, varied from 10% to 63%, with inconsistent reporting on interval time to reobstruction. Mortality, defined as death within 30 days of surgery, ranged from 0% to 32% and morbidity from 22% to 87%. The ability to tolerate oral feeding, despite recognition that this is an inadequate proxy for symptom resolution and quality of life, demonstrated success ranging from 30% to 100%.

The majority of obstructions in these studies were surgically addressed by proximal diversion (ileostomy and/or colostomy formation; 20%), bowel resection with anastomosis (48%), or bypass (38%), with most patients undergoing more than one intervention. The optimal surgical approach is dependent on disease extent and location, overall prognosis, nutritional status, and recent steroid/chemotherapy use. If

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Table 1. Differential Diagnosis of Bowel Obstruction in Patients With Peritoneal Carcinomatosis

Lesion	Etiology	Associated Conditions/Symptoms
Mechanical		
Extrinsic	Peritoneal carcinomatosis	Metastatic GI or ovarian tumors
	Adhesions	Prior surgery, peritonitis
	Hernia incarceration	Congenital or acquired
	Sclerosing mesenteritis	Prior surgery, malignancy (urogenital, GI adenocarcinoma, lymphoma)
	SMA syndrome	Rapid weight loss
	Volvulus	Chronic constipation, congenital aberrant attachments
Intrinsic or endoluminal	Large/small bowel neoplasms	CRC
	Anastomotic stricture	Prior intestinal surgery
	Ischemic stricture	Prior colon resection, PAD
	Radiation enteritis/fibrosis	Prior abdominal or pelvic radiation
	Foreign body	Medical device migration (PEG, jejunal tube)
	Intussusception	Small bowel tumor
	Feces	Chronic constipation, impaction
Functional		
Intramural	Bowel wall infiltration with or without edema	Gastric carcinoma (linitis plastica)
Drug induced	Anticholinergics, analgesics (opioids), antispasmodics, antihistamines, iron supplements, antiemetics (5-HT3 antagonists)	
Adynamic (paralytic) ileus	Paraneoplastic syndrome, mesenteric nerve infiltration, postoperative ileus	

NOTE. Adapted from Osteen et al.[8]

Abbreviations: CRC, colorectal carcinoma; 5-HT3, 5-hydroxytryptamine3 (serotonin) receptor; PAD, peripheral artery disease; PEG, percutaneous endoscopic gastrostomy; SMA, superior mesenteric artery.

feasible, bowel resection with anastomosis or internal bypass leads is preferred over a diverting ileostomy, because the latter may be associated with high-volume output, dehydration, and electrolyte imbalance due to a proximal location. In general, surgical intervention for palliative pain control is not recommended, given the availability of less-invasive options. The multiple caveats and ill-defined recommendations for appropriate surgical intervention further highlight the necessity for a multidisciplinary approach to care and the importance of early discussions of advanced directive planning.

NONOPERATIVE PROCEDURES

Malignant gastric outlet obstruction is usually related to duodenal obstruction from pancreatic cancer in the Western world, whereas invasive gastric carcinoma is the primary etiology in Asian populations. Although surgical bypass with anastomosis remains the preferred intervention for gastric outlet obstruction in patients with adequate life expectancies, for those with short expected survival (< 6 months), studies suggest endoscopic placement of self-expanding metal stents are comparable.[13] In patients with metastatic colorectal cancer, pancreatic cancer, and gastric cancer, clinical resolution of MBO was demonstrated in approximately 90% of patients who underwent duodenal stenting, with similar outcomes between obstructions due to primary tumor and peritoneal carcinomatosis.[14] Although stenting has been associated with less morbidity, mortality, and cost, recurrent obstruction requiring reintervention occurs in up to 40% of patients. Therefore, in select patients with peritoneal carcinomatosis limited to a single transition point proximal to the ligament of Treitz and lack of extensive peritoneal involvement, stenting may provide a valuable therapeutic option with a lower overall morbidity and

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mortality compared with surgical bypass. However, these should be performed at high-volume centers with expertise in advanced endoscopy and surgical back-up in case of a complication, such as perforation.

In patients with intractable symptoms, placement of a nasogastric tube (NGT) or venting gastrostomy should be considered to provide relief. Adverse effects associated with NGTs are generally limited to mild discomfort related to placement, but long-term placement increases the risk of more serious events, including aspiration pneumonitis, mucosal ulceration, pharyngitis, and sinusitis. NGT removal is recommended when secretions are reduced to $<$ 1 L in 24 hours. When removal is not feasible, venting gastrostomy placement (via endoscopic or interventional radiologic guidance) is a reasonable longer-term alternative.[9] Complications of venting gastrostomy include peristomal leakage, hemorrhage, cellulitis, clogging or dislodgement of the tube, and, rarely, pneumoperitoneum and peritonitis. If there is a contraindication to conventional venting gastrostomy (ie, ascites), a surgical gastrostomy can be considered. Interestingly, a recent small study demonstrated feasibility with minimal complications using a percutaneous transesophageal approach in patients with ascites.[15] Palliative venting gastrostomy placement should be considered early, because safety and use are worse with a delayed intervention.[16]

MEDICAL MANAGEMENT

Medical management, including antimotility, antisecretory, and antiemetic drugs, represents the mainstay intervention for symptomatic MBO. Spontaneous resolution of MBO occurs within 7 days for nearly one third of patients, but relapse of obstructive symptoms occurs in roughly 72%.[17] The use of corticosteroids (dexamethasone 4 to 12 mg daily) is hypothesized to operate through anti-inflammatory effects on tumor and bowel wall, indirect analgesia secondary to minimizing distension, and providing central antiemetic effects.[9] Multiple small, nonrandomized studies and a large meta-analysis have demonstrated short-term (1 month) clinical resolution of MBO secondary to GI and ovarian cancers with minimal toxicity, although no survival benefit was observed.[18] Although no conclusive recommendations regarding specific steroid dose, route, and duration of therapy can be offered, if a surgical bypass intervention is anticipated, steroid avoidance can decrease postoperative anastomotic and infectious complications.

Optimal management of nausea and vomiting involves targeting various central and peripheral receptors (eg, dopamine, acetylcholine, and 5-hydroxytryptamine-3 [5-HT3]), although superiority of any particular drug is based largely on expert consensus.[9,19] In patients with a partial bowel obstruction, prokinetic agents (eg, metoclopramide 10 mg intravenously [IV] every 4 hours) are considered an acceptable first-line treatment but should be avoided in those with a complete obstruction (ie, continuous rather than intermittent vomiting with or without obstipation). The use of selective dopamine (D2) antagonists (eg, haloperidol 0.5 to 5 mg IV four times a day) is another reasonable option, although no randomized data support this practice.[20] Olanzapine, an atypical antipsychotic, has been validated in both acute and chronic nausea in the palliative setting of advanced-stage malignancy, with negligible treatment-associated toxicity. Studies have shown olanzapine effectively reduces nausea and vomiting in patients with peritoneal carcinomatosis[21] and incomplete bowel obstruction[22] and demonstrated superiority over metoclopramide in controlling breakthrough nausea and emesis associated with highly emetogenic chemotherapy.[23] The use of 5-HT3 receptor antagonists (eg, ondansetron 8 mg IV three times a day) is not well studied in MBO; however, in cases of intractable emesis, a trial could be considered. Although physicians may have a preference on the basis of experience, each unique patient may require a combination of agents to palliate symptoms while minimizing adverse effects.

Initial medical management should also include an anticholinergic drug to reduce intestinal secretions, motility, and associated visceral pain. Scopolamine is a commonly used agent in the palliative setting of malignant bowel obstruction because it can be administered through a transdermal patch, although its ability to cross the blood-brain barrier increases the risk of somnolence and confusion. Pharmacologically similar to scopolamine, glycopyrrolate (0.1 to 0.2 mg IV twice a day) is an ideal first-line option, because its quaternary amine structure limits diffusion across the blood-brain barrier, minimizing sedation and mental status changes.[24] Reducing GI secretions may also include gastric acid suppression with proton-pump inhibitors and histamine (H_2) receptor antagonists. Although no randomized studies have evaluated benefit in MBO, a pooled meta-analysis demonstrated that ranitidine (H_2-blocker) was superior to proton-pump inhibitors and placebo in decreasing gastric secretion volumes in perioperative patients with MBO.[25]

Somatostatin analogs (SSA) inhibit the release and action of multiple hormones, reducing secretions, peristalsis, and splanchnic blood flow while enhancing water and electrolyte absorption. Several studies have suggested superiority of SSA (octreotide) to anticholinergic drugs in reducing vomiting and

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intestinal secretions and allowing higher rates of NGT removal, with up to 60% success rates reported.[26] Octreotide may be administered by subcutaneous (SC) bolus or continuous SC infusion. Its duration of activity is approximately 6 to 12 hours, with an average half-life elimination of 1.8 hours, thus necessitating a multiple daily dosing schedule. However, a paucity of well-designed randomized studies has left optimal timing of SSA initiation, dosing, and duration of therapy open for interpretation, warranting additional exploration with comparative trials with validated end points.[27] Obita et al[28] conducted a comprehensive systematic review of seven randomized controlled trials (RCTs) comparing SSA (eg, octreotide 200 to 900 μg SC twice a day to three times a day or 300 μg/d via continuous infusion) to placebo or other pharmacologic agents in MBO. The authors identified five trials with low-level evidence suggesting a benefit of SSAs, whereas two trials with higher-level evidence failed to demonstrate benefit. An important clinical consideration is the interval from onset to symptom relief. Two RCTs comparing octreotide to scopolamine demonstrated maximum SSA clinical benefit before treatment day 3, with no additional gains beyond day 6.[24] Thus, after an empiric trial, if there is no observable symptom improvement, SSA discontinuation is reasonable.[26] For those exhibiting clinical improvement, SSA maintenance with long-acting monthly octreotide offers clinical convenience.[29]

MALIGNANT ASCITES

Malignant ascites commonly presents with abdominal distention and pain, early satiety, and dyspnea. Once symptomatic, life expectancy typically ranges from weeks to a few months.[30] The multifactorial pathophysiology involves vascular epithelial growth factor–induced vascular permeability, lymphatic obstruction, portal hypertension, and hypoalbuminemia. Identification of malignant cells in ascitic fluid is a critical step in refining the differential diagnosis. However, less than two thirds of confirmed cases of malignant ascites are a direct result of peritoneal carcinomatosis; the remaining cases are secondary to other etiologies, all of which are less frequently associated with positive ascites cytology (Fig 1).[31] The overall sensitivity of cytology for malignant cells is 58% to 75% and varies depending on the ascitic volume processed and primary tumor origin.[32] The diagnostic accuracy is significantly improved with large-volume paracentesis and immunohistochemical staining. Sensitivity for positive cytology can be increased to 93% and 97% when two and three samples (50 mL/tube) are sent for analysis, respectively.[31] In addition, fluid should undergo routine laboratory evaluation (Fig 1). For low-volume ascites, the use of ultrasonography guidance can decrease procedural complications.[33]

Management of malignant ascites involves large-volume paracentesis and diuretics, although both provide only transient symptom relief.[34] To date, no randomized studies have evaluated diuretics in the setting of malignant ascites, with recommendations largely extrapolated from studies conducted in cirrhosis. Believed to be due to the limited role of the renin-angiotensin-aldosterone axis in the pathophysiology of malignant ascites, observational studies report modest diuretic success rates (< 40%) in peritoneal carcinomatosis-related ascites management.[34] In addition, the use of diuretics for

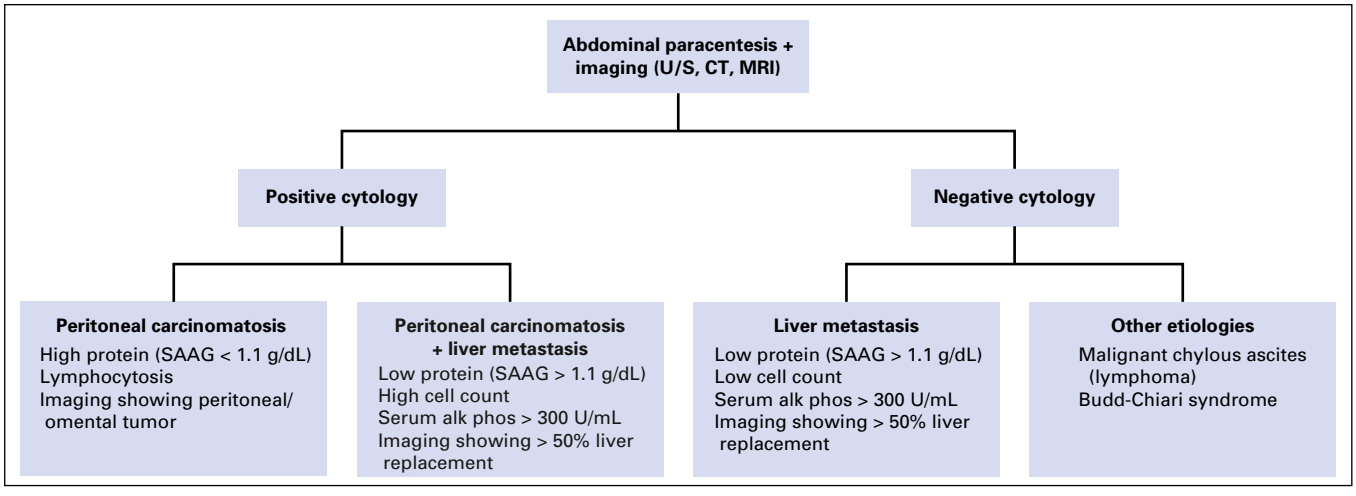

Fig 1. Paracentesis and fluid evaluation of ascites in patients with malignancy. alk phos, alkaline phosphatase; CT, computed tomography; MRI, magnetic resonance imaging; SAAG, serum-ascites albumin gradient; U/S, ultrasound.

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peritoneal carcinomatosis has been associated with poor patient outcomes, with up to one third of patients with peritoneal carcinomatosis–related ascites developing acute renal failure or symptomatic hypotension while failing to adequately mobilize third-spaced fluid, likely related to low oncotic pressures seen in advanced malignancy.[35] For recurrent symptomatic ascites, an intraperitoneal tunneled catheter can be placed under locoregional anesthesia with limited morbidity.[36] Contraindications to indwelling catheter placement include loculated ascites, infectious peritonitis, and uncorrected coagulopathy. Interestingly, several small series have reported resolution of ascites, reduction in symptoms, and improved quality of life in patients receiving laparoscopic intraperitoneal chemotherapy without cytoreduction. Alternative therapies currently under investigation include antiangiogenic agents, radioimmunotherapy, and targeted agents such as catumaxomab, a bispecific antibody to epithelial adhesion molecule (EpCAM) and the T-cell antigen CD3.[30]

NUTRITION

Malnutrition and cachexia are prototypical manifestations of advanced-stage cancer and are frequently exaggerated by concurrent pain, malaise, depression, mucositis, nausea, and early satiety. A declining nutritional state with unintentional weight loss strongly correlates with prolonged hospitalizations, postoperative complications, increased toxicities and reduced response to chemotherapy, and poor overall survival.[37] Emotional duress can drive caretakers to pressure physicians into initiating artificial parenteral or enteral feeding to meet caloric requirements, despite several trials failing to demonstrate significant improvements in lean body weight, fatigue, quality of life, or survival.[4] Rather, this nutritional support often results in increased health care expenditures, infectious and metabolic complications, and delays in appropriate transition to supportive care in terminal situations.[38,39]

In general, enteral feedings are in almost all situations preferable to parenteral nutrition. However, because peritoneal carcinomatosis frequently elicits a nonfunctional bowel, the controversies of parenteral nutrition rather than oral alimentation are discussed. Routine parenteral nutrition for patients with MBO, as with most end-stage cancers, is generally discouraged by professional societies, although guidelines support the use of parenteral nutrition in patients with cancer with a life expectancy $>$ 3 months who cannot tolerate oral or enteral tube feeding.[40] However, in patients with MBO supplemented with parenteral nutrition, a large meta-analysis demonstrated 3- and 6-month mortality rates of 55% and 76%, respectively.[37] These outcomes highlight the clinical challenge of identifying patients who will survive long enough to benefit from parenteral nutrition. In one representative study, patients with the combination of hypoalbuminemia, poor performance status, pain, vomiting, and decreased serum cholinesterase levels failed to demonstrate a median survival long enough ($<$ 45 days) to warrant parenteral nutrition (Table 2).[41,42] However, the pragmatic value of this approach was limited by low sensitivity, identifying only 21% of patients who survived $>$ 60 days.[41]

Although intravenous fluids are routine care for most bowel obstructions, data exist to limit intravenous fluids in MBO because of the risks of voluminous extracellular fluid expansion in cachexia, ascites exacerbation, and increased GI secretions.[43] Several studies demonstrate that routine artificial IV hydration does not improve patient outcomes, although multiple ethical analyses reviewing arguments for and against the appropriateness of artificial hydration conclude that patient and family preference is an important consideration.[43] The limitations of artificial IV hydration were highlighted in an RCT of 129 unselected hospice patients, randomly assigned to either intravenous hydration (1,000 mL over 24 hours) or placebo (100 mL). There were no differences between treatment and control arms in dehydration symptoms or delirium scores, at day 4 or day 7 and no statistically significant difference in overall survival (median, 21 *v* 15 days; $P = .83$).[44] An important limitation of this study was the exclusion of

Table 2. Factors Associated With Limited Benefit for Parenteral Nutrition in Patients With Peritoneal Carcinomatosis

Characteristics
Age $>$ 62 years
Recent weight gain as a result of ascites or anasarca
Albumin $\leq$ 2.8 (g/dL)
Lymphocyte count $<$ 1,187 cells/μL
Karnofsky Performance Status score $\leq$ 40
Pain requiring daily use of analgesia
Vomiting at least one episode per day for 7 consecutive days

NOTE. Peritoneal carcinomatosis defined as survival $<$ 30 days from the initiation of parenteral nutrition. Adapted from Santarpia et al.[41]

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severely dehydrated patients (ie, hemodynamic instability, altered mental status), because there may be acute survival benefits and improvement of delirium using artificial IV hydration in this population. Thus, the risks and benefits should be discussed with the patient and their family caretakers and considered in the context of their stated preferences, rather than decided by a standardized protocol for artificial intravenous hydration.

PAIN CONTROL

Pain associated with peritoneal carcinomatosis is multifactorial, related to the anatomic proximity of tumor to surrounding visceral structures, and is often exacerbated by bowel obstruction and ascites. The mainstay analgesic approach is commonly opioids because of their acceptable safety profile, diverse administration routes, therapeutic range, and efficacy against most mechanisms of pain (eg, somatic, visceral, and neuropathic).[45] Despite the diversity of pharmaceutical agents with varying mechanisms of action, pain control for peritoneal carcinomatosis remains a clinical challenge, namely due to the common adverse effects of constipation, sedation, and nausea.

In general, morphine is considered the prototypical opioid, used as the standardized comparative agent for dose conversion calculations and recommend as the first-line agent for cancer pain management.[45] Inherent variability in metabolism and response mechanisms to opioids make them unpredictable as to which individuals will experience a more favorable balance between analgesia and toxicity with any specific agent. Such pharmacogenomic differences provide a foundation for future efforts in personalized cancer pain management.[46]

Opioid-induced constipation (OIC) generally does not improve with development of analgesic tolerance. The presence of predisposing risk factors for alimentary tract dysfunction in peritoneal carcinomatosis, including immobility, malnutrition, electrolyte disturbances, neuropathies, advanced age, and concurrent use of additional antimotility agents (eg, anticholinergics), justifies routine use of an empiric bowel regimen in these patients. Although numerous laxatives are available for OIC, a comparative meta-analysis failed to identify a singularly superior agent.[47] Conventionally, clinicians should initiate a stool softener (docusate) and stimulant laxative (senna). If an inadequate response is observed, adding an osmotic agent (lactulose or polyethylene glycol) is a reasonable next step.

For refractory cases of OIC in the absence of MBO, consideration includes methylnaltrexone, an injectable peripheral opioid receptor antagonist with limited ability to traverse the blood-brain barrier. A recent meta-analysis of 14 trials (4,101 patients) demonstrated superior outcomes of μ-opioid antagonists, including methylnaltrexone and oral naloxone, compared with placebo for the treatment of OIC, although the majority of enrolled patients had chronic pain not related to malignancy.[48] Encouraging data on a combination oral therapy (naloxone and oxycodone) suggests improvement in OIC without compromising analgesic efficacy compared with oxycodone alone.[49] Complementary oral agents that have been efficacious in studies of patients with nonmalignant pain and resultant OIC are lubiprostone (chloride channel activator)[50] and naloxegol (pegylated naloxone).[51] However, all of these agents are contraindicated in MBO and should be avoided if obstruction is suspected, because severe abdominal colic and bowel perforation have been reported.[52,53]

Opioid-induced mental status changes, including somnolence and confusion, contribute to anorexia and reduced performance status. For patients with relatively well-controlled pain, empiric narcotic dose reduction is a reasonable first step to address mental status changes. If sustaining adequate analgesia is problematic, switching classes of opioids may alleviate mental clouding, or adding adjuvant co-analgesics (ie, steroids, antidepressants, topical and neuropathic drugs) may offer opioid-sparing pain control.[54] Alternatively, an empiric trial of psychostimulants (eg, methylphenidate 10 to 20 mg twice a day) may offer modest improvements in illness-related fatigue and opioid-induced lethargy, although the supporting evidence is largely based on anecdotal and retrospective data.[55]

For opioid-associated nausea, gradual dose titration is preferred. For those experiencing persistent nausea, first-line therapy with dopamine (eg, prochlorperazine or metoclopramide) and 5-HT3 (eg, ondansetron) antagonists is recommended.[56] For refractory nausea, a trial of antipsychotics (eg, risperidone or olanzapine) would be a rational option, recognizing that nausea in patients with MBO is likely multifactorial.[57]

PALLIATIVE CARE

The presence of peritoneal carcinomatosis and malignant bowel obstruction represents terminal complications of advanced GI cancer, and these patients tend to have a substantial symptom burden and may receive aggressive care at the end of life. There is a growing body of literature to support the latest clinical guidelines from the National Comprehensive Cancer Network (NCCN) and ASCO, recommending early integration of

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interdisciplinary palliative care services for patients with advanced, end-stage malignancy. Although additional research is required to further define optimal palliative care delivery models, multiple large clinical trials have demonstrated that early implementation of palliative care reduces depression, decreases financial and resource burdens, improves patient satisfaction and quality of life, and may even prolong survival.[58-63] In addition to improved patient and caregiver outcomes, it is noteworthy that there were no reported adverse events in any of the trials assessing early palliative intervention.

In conclusion, the oncologic condition of peritoneal carcinomatosis with associated symptoms is a common clinical challenge for providers and requires a multidisciplinary approach for successful palliation. Even with multidisciplinary care, innovative therapeutic approaches, and adequate caloric provision, this clinical condition typically represents a terminal event in the journey of the patient with cancer. Early palliative care involvement to positively affect quality of life and balance appropriate family and caregiver expectations for patients and their families is crucial. JOP

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Authors' Disclosures of Potential Conflicts of Interest

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References

1. Loupakis F, Cremolini C, Masi G, et al: Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. N Engl J Med 371:1609-1618, 2014

2. Wilke H, Muro K, Van Cutsem E, et al: Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): A double-blind, randomised phase 3 trial. Lancet Oncol 15:1224-1235, 2014

3. Brooks GA, Abrams TA, Meyerhardt JA, et al: Identification of potentially avoidable hospitalizations in patients with GI cancer. J Clin Oncol 32:496-503, 2014

4. Lambert LA: Looking up: Recent advances in understanding and treating peritoneal carcinomatosis. CA Cancer J Clin 65:284-298, 2015

5. National Comprehensive Cancer Network: Clinical practice guidelines in oncology: Colon cancer (version 2.2017). http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

6. Anthony T, Baron T, Mercadante S, et al: Report of the clinical protocol committee: Development of randomized trials for malignant bowel obstruction. J Pain Symptom Manage 34:S49-S59, 2007 (suppl 1)

7. Alese OB, Kim S, Chen Z, et al: Management patterns and predictors of mortality among US patients with cancer hospitalized for malignant bowel obstruction. Cancer 121:1772-1778, 2015

8. Osteen RT, Guyton S, Steele G Jr, et al: Malignant intestinal obstruction. Surgery 87:611-615, 1980

9. Laval G, Marcelin-Benazech B, Guirimand F, et al: Recommendations for bowel obstruction with peritoneal carcinomatosis. J Pain Symptom Manage 48:75-91, 2014

10. Koo DJ, Goring TN, Pinard K-A, et al: Malignant bowel obstruction in advanced cancer. Hosp Med Clin 5:413-424, 2016

11. Bristow RE, Duska LR, Lambrou NC, et al: A model for predicting surgical outcome in patients with advanced ovarian carcinoma using computed tomography. Cancer 89:1532-1540, 2000

12. Cousins SE, Tempest E, Feuer DJ: Surgery for the resolution of symptoms in malignant bowel obstruction in advanced gynaecological and gastrointestinal cancer. Cochrane Database Syst Rev 1:CD002764, 2016

13. Jeurnink SM, Steyerberg EW, van Hooft JE, et al: Surgical gastrojejunostomy or endoscopic stent placement for the palliation of malignant gastric outlet obstruction (SUSTENT study): A multicenter randomized trial. Gastrointest Endosc 71:490-499, 2010

14. Park CH, Park JC, Kim EH, et al: Impact of carcinomatosis and ascites status on long-term outcomes of palliative treatment for patients with gastric outlet obstruction caused by unresectable gastric cancer: Stent placement versus palliative gastrojejunostomy. Gastrointest Endosc 81:321-332, 2015

15. Singal AK, Dekovich AA, Tam AL, et al: Percutaneous transesophageal gastrostomy tube placement: An alternative to percutaneous endoscopic gastrostomy in patients with intra-abdominal metastasis. Gastrointest Endosc 71:402-406, 2010

16. Shaw C, Bassett RL, Fox PS, et al: Palliative venting gastrostomy in patients with malignant bowel obstruction and ascites. Ann Surg Oncol 20:497-505, 2013

17. Tuca A, Guell E, Martinez-Losada E, et al: Malignant bowel obstruction in advanced cancer patients: Epidemiology, management, and factors influencing spontaneous resolution. Cancer Manag Res 4:159-169, 2012

18. Feuer DJ, Broadley KE: Corticosteroids for the resolution of malignant bowel obstruction in advanced gynaecological and gastrointestinal cancer. Cochrane Database Syst Rev 2:CD001219, 2000

19. Davis MP, Hallerberg G, Palliative Medicine Study Group of the Multinational Association of Supportive Care in Cancer: A systematic review of the treatment of nausea and/or vomiting in cancer unrelated to chemotherapy or radiation. J Pain Symptom Manage 39:756-767, 2010

20. Murray-Brown F, Dorman S: Haloperidol for the treatment of nausea and vomiting in palliative care patients. Cochrane Database Syst Rev 11:CD006271, 2015

21. Murakami N, Tanabe K, Yamatani K, et al: Use of orally disintegrating olanzapine tablet for patients with cancerous peritonitis and postoperative gastric cancer receiving home palliative care [in Japanese]. Gan To Kagaku Ryoho 39:649-652, 2012

22. Kaneishi K, Kawabata M, Morita T: Olanzapine for the relief of nausea in patients with advanced cancer and incomplete bowel obstruction. J Pain Symptom Manage 44:604-607, 2012

23. Navari RM, Nagy CK, Gray SE: The use of olanzapine versus metoclopramide for the treatment of breakthrough chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. Support Care Cancer 21:1655-1663, 2013

24. Ripamonti C, Mercadante S, Groff L, et al: Role of octreotide, scopolamine butylbromide, and hydration in symptom control of patients with inoperable bowel obstruction and nasogastric tubes: A prospective randomized trial. J Pain Symptom Manage 19:23-34, 2000

25. Clark K, Lam L, Currow D: Reducing gastric secretions–a role for histamine 2 antagonists or proton pump inhibitors in malignant bowel obstruction? Support Care Cancer 17:1463-1468, 2009

26. Mercadante S, Porzio G: Octreotide for malignant bowel obstruction: Twenty years after. Crit Rev Oncol Hematol 83:388-392, 2012

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27. Hwang M, Pirrello R, Pu M, et al: Octreotide prescribing patterns in the palliation of symptomatic inoperable malignant bowel obstruction patients at a single US academic hospital. Support Care Cancer 21:2817-2824, 2013

28. Obita GP, Boland EG, Currow DC, et al: Somatostatin analogues compared to placebo and other pharmacological agents in the management of symptoms of inoperable malignant bowel obstruction: A systematic review. J Pain Symptom Manage 52:901-919.e1, 2016

29. Laval G, Rousselot H, Toussaint-Martel S, et al: SALTO: a randomized, multicenter study assessing octreotide LAR in inoperable bowel obstruction. Bull Cancer 99:E1-E9, 2012

30. Valle SJ, Alzahrani NA, Alzahrani SE, et al: Laparoscopic hyperthermic intraperitoneal chemotherapy (HIPEC) for refractory malignant ascites in patients unsuitable for cytoreductive surgery. Int J Surg 23:176-180, 2015

31. Giannini EG, Marabotto E, Savarino V, et al: Hepatocellular carcinoma in patients with cryptogenic cirrhosis. Clin Gastroenterol Hepatol 7:580-585, 2009

32. Decker D, Stratmann H, Springer W, et al: Benign and malignant cells in effusions: Diagnostic value of image DNA cytometry in comparison to cytological analysis. Pathol Res Pract 194:791-795, 1998

33. Lee YT, Ng EK, Hung LC, et al: Accuracy of endoscopic ultrasonography in diagnosing ascites and predicting peritoneal metastases in gastric cancer patients. Gut 54:1541-1545, 2005

34. Lee CW, Bociek G, Faught W: A survey of practice in management of malignant ascites. J Pain Symptom Manage 16:96-101, 1998

35. Pockros PJ, Esrason KT, Nguyen C, et al. Mobilization of malignant ascites with diuretics is dependent on ascitic fluid characteristics. Gastroenterology 1992;103:1302-1306

36. Burleigh J, Mehta Z, Ellison N: Tunneled indwelling catheters for malignant ascites #308. J Palliat Med 19:671-672, 2016

37. Naghibi M, Smith TR, Elia M: A systematic review with meta-analysis of survival, quality of life and cost-effectiveness of home parenteral nutrition in patients with inoperable malignant bowel obstruction. Clin Nutr 34:825-837, 2015

38. Gupta D, Lis CG, Granick J, et al: Malnutrition was associated with poor quality of life in colorectal cancer: A retrospective analysis. J Clin Epidemiol 59:704-709, 2006

39. Koretz RL, Avenell A, Lipman TO, et al: Does enteral nutrition affect clinical outcome? A systematic review of the randomized trials. Am J Gastroenterol 102:412-429, 2007; quiz 468

40. Bozzetti F, Arends J, Lundholm K, et al: ESPEN: ESPEN guidelines on parenteral nutrition: Non-surgical oncology. Clin Nutr 28:445-454, 2009

41. Santarpia L, Alfonsi L, Pasanisi F, et al: Predictive factors of survival in patients with peritoneal carcinomatosis on home parenteral nutrition. Nutrition 22:355-360, 2006

42. Bozzetti F: Nutritional support of the oncology patient. Crit Rev Oncol Hematol 87:172-200, 2013

43. Druml C, Ballmer PE, Druml W, et al: ESPEN guideline on ethical aspects of artificial nutrition and hydration. Clin Nutr 35:545-556, 2016

44. Bruera E, Hui D, Dalal S, et al. Parenteral hydration in patients with advanced cancer: A multicenter, double-blind, placebo-controlled randomized trial. J Clin Oncol 31:111-118, 2012

45. Quigley C. Opioids in people with cancer-related pain. BMJ Clin Evide 2008:2408, 2008

46. Crews KR, Gaedigk A, Dunnenberger HM, et al: Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther 95:376-382, 2014

47. Candy B, Jones L, Larkin PJ, et al: Laxatives for the management of constipation in people receiving palliative care. Cochrane Database Syst Rev 5:CD003448, 2015

48. Ford AC, Brenner DM, Schoenfeld PS: Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: Systematic review and meta-analysis. Am J Gastroenterol 108:1566-1574, 2013; quiz 1575

49. Burness CB, Keating GM: Oxycodone/naloxone prolonged-release: A review of its use in the management of chronic pain while counteracting opioid-induced constipation. Drugs 74:353-375, 2014

50. Cryer B, Katz S, Vallejo R, et al: A randomized study of lubiprostone for opioid-induced constipation in patients with chronic noncancer pain. Pain Med 15:1825-1834, 2014

51. Chey WD, Webster L, Sostek M, et al: Naloxegol for opioid-induced constipation in patients with noncancer pain. N Engl J Med 370:2387-2396, 2014

52. Centeno C, Carranza O, Zuriarrain Y, et al: A prospective study of methylnaltrexone for opioid-induced constipation in advanced illness: Should we use it or not? J Pain Symptom Manage 46:e1-e3, 2013

53. Thomas J, Karver S, Cooney GA, et al: Methylnaltrexone for opioid-induced constipation in advanced illness. N Engl J Med 358:2332-2343, 2008

54. Mercadante S, Portenoy RK: Opioid poorly-responsive cancer pain. Part 3. Clinical strategies to improve opioid responsiveness. J Pain Symptom Manage 21:338-354, 2001

55. Stone P, Minton O: European Palliative Care Research collaborative pain guidelines. Central side-effects management: What is the evidence to support best practice in the management of sedation, cognitive impairment and myoclonus? Palliat Med 25:431-441, 2011

56. Laugsand EA, Kaasa S, Klepstad P: Management of opioid-induced nausea and vomiting in cancer patients: Systematic review and evidence-based recommendations. Palliat Med 25:442-453, 2011

57. Okamoto Y, Tsuneto S, Matsuda Y, et al: A retrospective chart review of the antiemetic effectiveness of risperidone in refractory opioid-induced nausea and vomiting in advanced cancer patients. J Pain Symptom Manage 34:217-222, 2007

58. Bakitas M, Lyons KD, Hegel MT, et al: Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: The Project ENABLE II randomized controlled trial. JAMA 302:741-749, 2009

59. Bakitas MA, Tosteson TD, Li Z, et al: Early versus delayed initiation of concurrent palliative oncology care: Patient outcomes in the ENABLE III randomized controlled trial. J Clin Oncol 33:1438-1445, 2015

60. Temel JS, Greer JA, Muzikansky A, et al: Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 363:733-742, 2010

61. Temel JS, Greer JA, El-Jawahri A, et al. Effects of early integrated palliative care in patients with lung and GI cancer: A randomized clinical trial. J Clin Oncol 35:834-841, 2017

62. Ferrell BR, Temel JS, Temin S, et al: Integration of palliative care into standard oncology care: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 35:96-112, 2017

63. Zimmermann C, Swami N, Krzyzanowska M, et al: Early palliative care for patients with advanced cancer: A cluster-randomised controlled trial. Lancet 383:1721-1730, 2014

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Management of Malignant Bowel Obstruction Associated With GI Cancers

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